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Barriers of Mucosal Entry of HIV/SIV

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Abstract

Most new HIV infections, over 80%, occur through sexual transmission. During sexual transmission, the virus must bypass specific female and male reproductive tract anatomical barriers to encounter viable target cells. Understanding the generally efficient ability of these barrier to exclude HIV and the precise mechanisms of HIV translocation beyond these genital barriers is essential for vaccine and novel therapeutic development. In this review, we explore the mucosal, barriers of cervico-vaginal and penile tissues that comprise the female and male reproductive tracts. The unique cellular assemblies of the squamous and columnar epithelium are illustrated highlighting their structure and function. Each anatomical tissue offers a unique barrier to virus entry in healthy individuals. Unfortunately barrier dysfunction can lead to HIV transmission. How these diverse mucosal barriers have the potential to fail is considered, highlighting those anatomical areas that are postulated to offer a weaker barrier and are; therefore, more susceptible to viral ingress. Risk factors, such as sexually transmitted infections, microbiome dysbiosis, and high progesterone environments are also associated with increased acquisition of HIV. How these states may affect the integrity of mucosal barriers leading to HIV acquisition are discussed suggesting mechanisms of transmission and revealing potential targets for intervention.

Keywords

HIV infection; female reproductive tract; vaginal transmission; target cells; hormonal contraception; HIV risk

1. INTRODUCTION

More than 1.2 million people in the United States are living with human immunodeficiency virus (HIV), with approximately 40,000 persons in the United States becoming infected each year and approximately 12,000 persons dying each year due to HIV related complications [1, 2]. Worldwide, the story is even more devastating with an estimated 37 million people living with HIV, and over 2 million people becoming infected annually [1]. It is only through a complete understanding of the mechanisms behind HIV transmission, including the

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CONFLICT OF INTEREST

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identification of how the virus can bypass specific reproductive tract anatomical barriers, that such tragedies can be averted.

HIV is transmitted from person-to-person through infectious bodily fluids by three main routes of transmission. 1) percutaneous, usually through contaminated needles and blood products, 2) perinatal, or Mother-To-Child Transmission (MTCT), and 3) sexual transmission. The last two routes are defined as mucosal HIV transmission, with sexual transmission accounting for approximately 80% of all mucosal transmission events [1]. In the case of sexual transmission, the virus enters the vulnerable host by traversing the mucosal epithelial barriers of the cervico-vaginal, penile, or rectal tissues to reach a susceptible target cell expressing surface receptor CD4 and co-receptors R5 or X4 [3, 4]. It is the probability of these transmission events, after exposure to an infected individual, which defines HIV infectivity [5]. In the past, the generally agreed upon standard rate of infection for male-to-female sexual encounter with an infected partner is low at ~0.001 (1 transmission event in 1000 acts); however, this commonly cited value has been shown to grossly underestimate transmission events [6–8]. This is evident, as although male-to-female vaginal transmission of HIV has the lowest rate per coital act, it still accounts for the majority of new infections worldwide [6, 8]. However, the initial events in transmission that dictate whether infection occurs after vaginal HIV exposure remain under investigation.

Most of the time, in a healthy individual, the innate anatomical tissue barriers of the vagina provide robust barricades to HIV transmission and; therefore, prevent successful transmission. Aiding in the barrier properties of these tissues are various cellular proteins, such as tight junctions, desmosomes and adherens junctions. These protein networks are responsible for “holding together” adjacent cell membranes, decreasing tissue permeability; *i.e.*, preventing microbial translocation across mucosal barriers in the gut, and possibly the vagina. These networks even prevent small molecule passage between cells, and limit epithelial shearing [9–11]. There are also distinct differences amongst each structural barrier that HIV may come in contact with, with each tissue type providing a particular obstacle for the virus to overcome prior to establishing infection. The scope of this review will only cover cervico-vaginal and penile barriers, not rectal, although certain aspects of the columnar epithelium, described below, would apply.

1.1. Viral Barriers in the Female Reproductive Tract

The primary barriers of the Female Reproductive Tract (FRT) likely to contact infectious male secretions are cervico-vaginal epithelia. These anatomical barriers are the stratified squamous epithelia of the lower reproductive tract (ectocervix and vagina) and the simple columnar epithelia of the upper reproductive tract (endocervix) (Fig. 1). The squamous epithelium of the ectocervix and vagina of the lower FRT is a minimally-keratinizing, multi-layered structure, approximately 100–200 microns thick, where the corneal epithelial cells change from cuboidal to flattened morphologies during maturation (Fig. 1B, D–E). Once flattened, these cells comprise a layer of enucleated cells (stratum corneum) (Fig. 1B), which can be construed as an additional obstacle to pathogens. Due to the robustness of this squamous epithelium, it has been historically thought to offer a significant physical barrier to small molecule entry, such as HIV (Reviewed by [12]).

In contrast, the columnar epithelium of the upper FRT is a thin barrier, composed of a single layer of cuboidal epithelial cells, approximately 10 to 30 microns thick with a high concentration of HIV target cells in close proximity to the lumen (Fig. 1A, C) [12–14]. Although the columnar epithelium of the FRT is a considerably thinner barrier than the stratified squamous epithelium of the lower FRT, this area is ~15 times smaller than the vaginal vault [12]. Therefore, comparatively, its surface area only comprises a small portion of the total area exposed to virus-containing ejaculate. The endocervical epithelium is also unique in that it is composed of invaginated crypts that contain intra-epithelial goblet cells. These cells are responsible for producing cervical mucus that protect the columnar epithelium and create further protection from invading pathogens (Fig. 1A) [15, 16]. This protective characteristic of cervical mucus was illustrated by studies where HIV had a limited ability to enter the endocervical lumen in *in vivo* analyses, but not in *ex vivo* samples [17]. Experiments conducted using a mucin depleting enzyme in explant cultures revealed that when the mucus is degraded, virus more readily interacts with and is able penetrate the columnar epithelium of the upper FRT [17]. Additionally, not only has cervical mucus been demonstrated to impede the mobility of microorganisms to enhance barrier function, but it also has been shown to contain secretory IgAs, lactoferrin, lysozyme, and other antiviral proteins that may play a role in microbial defense [18].

Lastly, the Transformation Zone (TZ), otherwise known as the transitional zone, is the region where the simple columnar of the endocervix meets and transitions into the squamous epithelium of the ectocervix. The surface area of the transformation zone is very small and represents a very minor area of potential exposure. This area, like the thin endocervical barrier, is thought to be the area where HIV is likely to transverse, causing infection [12]. This is hypothesized mainly on the basis that in normal female FRT, this region has the highest number of HIV target cells, including a greater density of intra-epithelial target cells [19].

1.2. Viral Barriers in the Male Reproductive Tract

Much like the FRT, the Male Reproductive Tract (MRT) also consists of a myriad of types of anatomical barriers; however, the structure of the MRT is somewhat dependent on whether an individual is circumcised or not (Fig. 2). In a flaccid, non-circumcised man, the dry outer foreskin completely covers the glans and urethral opening (Fig. 2A). During erection, this foreskin is pulled back, thereby exposing the moist, subpreputial epithelia of the inner foreskin, urethral orifice, and glans (Fig. 2B) [20]. When erect, the outer foreskin retracts exposing the glans and urethral opening. In contrast, following circumcision, the majority of the inner foreskin epithelium is removed. This procedure leaves the glans exposed to the environment during both flaccid and erect states, resulting in the glans epithelial barrier transitioning to a more dry, keratinized epithelium (Fig. 2C–D) [21].

When intact and healthy, the tissues that comprise the MRT act as robust barricades to pathogens. Similar to the vaginal epithelium of the FRT, most penile epithelium, such as the inner foreskin, outer foreskin, and glans, are composed of a thick, multi-layered stratified squamous epithelium (Fig. 2E–H). In contrast to the FRT, the external MRT squamous tissues are protected by a superficial keratinized stratum corneum (Fig. 2E–G). The one

exception is the epithelium of the urethra, which is composed of three heterogeneous segments that range from a transitional epithelium, to a multi-layered, but much thinner, pseudo-stratified columnar structure, finally transforming to a stratified squamous epithelium at the external os (proximal to distal) (Fig. 2H). With the proximal portion of the urethra being composed of non-squamous epithelia, some postulate that these thin, easily traversable barriers may provide an accessible entry point for HIV in MRT [22, 23]. However, the urethra also contains the glands of Littre, which are periurethral glands that secrete mucus to line the tissue against the corrosiveness of urine [24]. Thus similar to the FRT, this mucus layer could offer an additional barrier to HIV infiltration and penetration.

1.3. When Barriers Fail – Where does HIV Entry Occur?

Despite it becoming increasingly clear that HIV transmission across mucosal tissues is inefficient, this does not mean that it cannot occur. In basic terms, for infection to occur following coitus, HIV must bypass the epithelial barriers of the FRT or MRT and gain access to target cells expressing the surface receptor CD4 and co-receptors R5 or X4 [3, 4]. However, how HIV traverses the intercellular junctions of epithelia to elicit infection remains a topic of debate. It is still uncertain which mechanism, or mechanisms, most accurately explains HIV *in vivo* transmission [12]. For virus traversing simple epithelial monolayers, current mechanistic-based theories posit transcytosis, dendritic cell translocation and entry through breaks and microabrasions (Fig. 3A-C) [25, 26]. Furthermore, concerning the stratified squamous epithelium, researchers have hypothesized transmission to occur by Langerhans cell uptake and transfer to viable target cells along with, once again, breaks and tears in the epithelial barrier (Fig. 3D-E) [12]. However, the specific tissues or mechanisms that provide the greatest barrier to HIV transmission, and how they may be maintained, remain still debated.

2. MECHANISMS OF SEXUAL HIV TRANSMISSION

2.1. Viral Transmission in the Female Reproductive Tract

Historically, the columnar epithelium of the upper Female Reproductive Tract (FRT) has been hypothesized to provide the most plausible route for HIV to access target cells due to the single celled nature of the barrier; however, various studies have elucidated that this is not the only location of HIV ingress. For example, studies on hysterectomized non-human primates have shown that SIV can establish infection when only the vaginal vault remains [27]. HIV cases have also been documented in women with Meyer-Rokitansky-Kuster-Hauser syndrome: a condition characterized by the congenital absence of a cervix and clinical studies have revealed that the use of a diaphragm, a device that covers the entirety of the endocervix, does not decrease HIV acquisition in women [28, 29]. Also of note, it is the vaginal squamous epithelium, and not the epithelium of upper FRT, that is initially in contact with infected male ejaculate. Additionally, although a robust and much thicker barrier than the endocervical simple columnar, both *ex vivo* explant and *in vivo* primate studies have revealed that this previously believed “impenetrable” layer can indeed be penetrated. For example, it has been shown that virus can penetrate into the layers of squamous epithelial cells, both *ex vivo* and *in vivo*, through interstitial percolation that follows a simple diffusion-based gradient, and most of the virions detected are within 10µm of the lumen

[17]. Importantly however, virions readily, and deeply penetrate the squamous barrier in those areas where epithelial integrity is compromised, and cellular junctions are either absent or degraded. This was studied in more detail by disrupting tight junction proteins using the calcium chelator EDTA in explant samples *ex vivo* [12, 17]. When EDTA was applied, a greater number of virions were seen to penetrate samples more readily, and to deeper depths, than when compared to non-treated cervical explant samples, suggesting that viral depth is directly proportional to epithelial permeability and inversely proportional to the robustness of cellular junctions [17]. Moreover, in a separate study, Stieh and Maric *et al.* utilizing a replication incompetent viral vector (LICH) in macaques demonstrated that virions were able to bypass the thick stratified squamous epithelium to preferentially infect those cells in both the vaginal and ectocervical regions. However, and importantly, this same study also illustrated infected cells throughout the entire FRT, including the ovaries and uterus. These data suggest that both the upper and lower FRT are susceptible to viral infection, thereby indicating that virus entry can occur throughout the entire FRT when epithelial barriers are compromised [30].

2.2. Viral Transmission in the Male Reproductive Tract

As already mentioned, a male's circumcision status plays a large role in the presence of anatomical barriers the virus must traverse, which can influence HIV transmission and susceptibility. In practice, this has been denoted by various male medical circumcision (MMC) trials that have shown to reduce the risk of HIV infection by 50–60% in circumcised individuals [31–33]. Due to such protective effects of MMC, it was initially recorded that the keratinized stratum corneum of the inner foreskin was thinner, offering less of a barrier than the outer foreskin, thereby suggesting inner foreskin as the most probable area for HIV transmission [34, 35]. However, these early studies used subjective measuring techniques. Subsequent studies, using specifically generated objective algorithms to measure keratin differences between the outer and inner foreskin, indicate that there are insignificant differences at these sites, thereby refuting keratinized barrier thickness as a possible mechanism of increased HIV transmission [36, 37].

Regardless, although inner foreskin thickness may not offer a thinner barrier for HIV entry does not mean it is not susceptible. For example, some have postulated that HIV transmission is determinate on surface area of tissue virus comes in contact with. In other words, the higher the surface area of tissue, especially one with more target cells such as foreskin in uncircumcised individuals, the more likely HIV acquisition is to occur [38]. Additionally, one study has suggested that the resident Langerhans cells in the inner foreskin of uncircumcised men are better able to sample the external environment than those found in the outer foreskin [39]. Lastly, it has been documented that in foreskin explants that compare viral penetration differences between circumcised and uncircumcised tissues after 24 hours, HIV was found to more easily penetrate the inner foreskin, along with the glans of uncircumcised men [21]. Collectively, these data may offer a biological explanation for the observed protective effects of MMC.

Along with the inner foreskin, the glans and urethra are also thought to be anatomical areas that may offer a weaker barrier for HIV entry in uncircumcised individuals. For example, in

these men, when erection is complete and the dry outer foreskin takes its place back over the glans and urethra, HIV virions and donor-supplied infected cells may become caught within the tissue folds, thereby increasing the chance for the virus to cross these barriers [22, 40]. In contrast, during the process of MMC, the majority of the foreskin epithelium is excised. This tissue removal leaves the glans exposed to the environment and has been proposed to result in the glans barrier transitioning from a moist to a dry keratinized epithelium and; therefore, providing a greater barrier to HIV penetration [21]. Convincingly, this has been depicted in a study utilizing whole cadaveric penile explant samples. When cell-free virus was applied to these samples, 4 hrs post exposure; a significantly greater number of HIV virions were found in glans tissues of uncircumcised individuals. In contrast, in circumcised individuals, more virions were found to interact with the inner foreskin remnants and less virions were found penetrating the glans [21]. These data confirm that, in uncircumcised individuals, the wet, subpreputial epithelium of the glans and inner foreskin may provide a weaker barrier to infectious microorganisms, including HIV [20, 41, 42].

However, and most importantly, these studies are still in their infancy and more research needs to be conducted. Precisely which tissues or conditions that disrupt normally protective barrier functions against HIV, and/or what mechanisms the virus exploits to breach these epithelia, remain essentially unknown, as progress remains impeded due to the lack of availability of pertinent human tissue samples. One way around this caveat is through the use of non-human primate models and interestingly, much like the FRT, new evidence is now suggesting that HIV entry can occur throughout the MRT, and like the FRT, without preference for a particular tissue site. Using a non-human primate penile transmission model, Ma *et al.* [43] were able to illustrate that penile SIV transmission occurred in numerous areas of the macaque penis, including the glans, inner and outer foreskin and urethra. These data clearly suggest that although certain anatomical tissues may be more permissible to virus entry than others, the entire MRT may be susceptible; however, how these data correlate to human studies remains unknown.

3. ADDITIONAL RISK FACTORS

Although the rate of HIV transmission is low per heterosexual encounter, there are cofactors that can increase this rate, referred to as risk factors [6]. For example, transmission rates can be greatly affected by the stage of infection and viral load, along with the age of the individual [44, 45]. One of the greatest risk factors associated with HIV transmission is the presence of other Sexually Transmitted Infections (STIs) [46, 47]. This is particularly evident when considering the synergistic relationship between concurrent STIs and increased HIV transmission rates in both women and men [6, 48–51]. For example, specific ulcerative STIs, such as herpes simplex virus 2 (HSV-2), are known to increase HIV susceptibility [52–56]. Whether this is due to HSV2-induced microabrasions of reproductive epithelial barriers or to underlying genital inflammation is still unknown [57, 58]. Some propose that physical breaches, decreased tissue integrity, and breaks in the squamous epithelium barrier caused by HSV-2 may expose target cells in the lamina propria directly to HIV during heterosexual transmission [59, 60]. At the same time, there is also evidence that not only ulcerative STIs, but also inflammatory STIs, are associated with increased HIV acquisition, suggesting that inflammation, rather than just physical breaches, may also affect

tissue barrier properties and play a role in increased access to target cells [61–63]. This is consistent with our previous studies demonstrating that alterations in hormone levels in the FRT especially may increase the accessibility of viral target cells in the vaginal epithelium [64].

3.1 The Vaginal Microbiome

It is hypothesized that the microbiome also influences the barrier function of the FRT and may be associated with increased HIV acquisition. Although this particular field is still in its infancy, recent data suggests that there is a link between the increased diversity of FRT microbiota and increased vaginal immune responses. For example, the higher diversity of non-*Lactobacillus* spp. may negatively impact the FRT in relation to HIV acquisition. This is thought to be due to the recruitment of CD4+ target cells and an increase in pro-inflammatory cytokines [65, 66]. The microbiome may play a role in the barrier function of the MRT as well. In uncircumcised men, the subpreputial area has been demonstrated to contain a number of pro-inflammatory bacteria that may enhance HIV transmission and acquisition at neighboring mucosal sites [67–69]. However, how these microorganisms affect the natural anatomical barriers of reproductive tissues to increase HIV entry has yet to be elucidated. A possible explanation is that these microorganisms are able to cause damage the natural tissue barriers of both the FRT and MRT, possibly through the disruption of cellular junctions [70]. After this damage occurs, there is a CCL20/CCR6 recruitment of Th17 cells, the likely initial target of HIV, in order to maintain the epithelial integrity of these tissues. This influx of Th17 cells may also result in foci of infectable cells in areas of compromised tissue barriers from these or other factors [71, 72]. Unfortunately, the exact nature of damage that is caused to these tissues by the microbiome is still an area that needs to be explored more thoroughly.

3.2 Endogenous and Exogenous Hormonal Effects on HIV Transmission

Lastly, another possible risk factor associated with increased HIV transmission is the effects of endogenous and exogenous hormones. Historically, macaque FRT models have revealed that progestin-dominant hormonal states, both endogenous and exogenous, thin the squamous epithelial barriers of the lower FRT and can increase the efficiency of SIV/SHIV acquisition after vaginal challenge [73–76]. During the menstrual cycle, this is due to an increase in endogenous estrogen during the follicular phase that leads to proliferation and thickening of the squamous epithelia of both the vagina and ectocervix. In contrast, an increase in progesterone results in thinning of the squamous epithelia during the luteal phase [77]. Exogenous hormones, such as the progestin-containing injectable contraceptive, depot-medroxyprogesterone acetate (DMPA), mimics the luteal state, also resulting in thinning of these barriers [73, 78, 79].

However, not only does the thickness of the squamous epithelium change during high progesterone environments, but so do the properties of the mucus barrier that covers the simple columnar of the endocervix. During the initial days of the follicular phase, both estrogen and progesterone levels are low, cervical mucus is relatively thick. This is believed to be due to diminishing levels of estrogen, as it enhances mucin production from goblet cells [18, 80]. As the menstrual cycle approaches ovulation and estrogen levels increase,

cervical mucus becomes less viscous. Towards the luteal stage of the menstrual cycle, when progesterone levels increase, it acts as a secretagogue on goblet cells, resulting in the mucus becoming thick, yet with expressional fluctuations in the different types of mucins and their glycosylation status [81–83].

Studies have assessed the histological influence of various hormone states, including those that occur during the menstrual cycle and after DMPA injection on the vaginal epithelial architecture in non-human primates. These data illustrated that DMPA and the natural menstrual cycle luteal phase have a similar impact on the vaginal epithelium [64]. Specifically, both hormonal states result in a shedding of the non-viable stratum corneum layer of the vagina resulting in a thinner vaginal epithelium. This thinning results in a decreased barrier to protect HIV susceptible cells from being infected. Additionally, thinning of the epithelium increases the number of HIV CD4+ and CD68+ target cells close to the tissue surface compared to vaginal tissue that retains the outer layer of cornified epithelial cells (*i.e.*, in the stratum corneum during the non-luteal phase and without DMPA administration). Finally, when HIV was introduced to vaginal mucus samples from non-human primates receiving DMPA, the mucus barrier was unable to greatly hinder the transport of virus compared to those animals that were DMPA-free. In other words, during DMPA use, or during the luteal phase of the menstrual cycle, the natural barriers of the female reproductive tract are compromised, thereby allowing for a greater opportunity of HIV acquisition [64].

Unfortunately, how these data translate to women is still unknown. When assessing how the natural menstrual cycle, and endogenous hormones, affect the barriers of the FRT and influence HIV transmission, most research conducted with human vaginal biopsies have suggested the probability of a increase in HIV acquisition during the luteal phase, but nothing has proven statistically significant [79]. More convincing is the case for exogenous hormones, as other studies have suggested that high progesterone contraceptive use, such as DMPA has an increased effect on HIV-1 acquisition [84–89]. Further, and as in non-human primates, studies have also depicted an increase in intra-epithelial vaginal target cells amongst women initiating such birth control modalities [79, 90]. Lastly, these exogenous hormones have also been found to directly affect the cellular junctions of the vaginal anatomical barriers. For example, a recent study by Quispe Calla *et al.*, [91] demonstrated, in both mice and in human ectocervical biopsies, increased epithelial inflammatory responses one-month post DMPA with a decrease in desmosomal proteins. These data suggests a degradation of the natural squamous barrier, which may result in decreased protection to invading microorganisms [91]. Overall; however, these studies are still a topic of debate as other research has purported that effects of exogenous and endogenous progesterone in inducing epithelial thinning are minimal, and have little affects on epithelial barrier properties, and virus transmission in humans [92–98]. Although the evidence is stacking in favor of endogenous and exogenous affecting the barrier properties of the epithelium, it is obvious that more research is needed.

CONCLUSION

It is evident that maintaining mucosal barrier integrity is important in preventing HIV transmission, as all of these combined data highlight that under healthy conditions, both the upper and lower FRT and MRT barriers pose a significant challenge for virus entry. It is only when these barriers are disrupted and fail that HIV is able to bypass the epithelium to infect a viable target cell. Additionally, caution should be taken when an individual harbors one or more of the various risk factors, such as STIs, the microbiome, and endogenous and exogenous hormones, as each of these factors may affect cellular junctions and therefore, the protective nature of the natural reproductive tract barriers. However, there is still much research needed on these barriers and their ability to allow or impede virus entry. To date, due to the difficulty of obtaining certain penile tissue samples, the FRT has been more extensively studied than the MRT; however, in both environments, more information is needed not only on what specific tissues the virus may more readily enter, but also on those environmental factors that may alter these tissue barriers. For example, it is still being explored how hormonal changes alter the vaginal epithelium in humans, and how the microbiome influences the barrier properties of cervical, cervico-vaginal, and periurethral mucus. It is only through a complete understanding of how and when HIV traverses such anatomical barriers that HIV preventative measures can be enacted.

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Fig. (1).

Histological Structures of the Female Reproductive Tract; A Macroscopic (left) and Microscopic View (middle, right) of the FRT: **(A)**. Upper reproductive tract. Includes the endocervix and uterus. Tissue is primarily composed of simple columnar epithelium, 10–30 microns thick. The simple columnar of the endocervix also contains goblet cells that are responsible for cervical mucus production (green). **(B)**. Lower reproductive tract. Includes the ectocervix and vagina. Tissue is composed of stratified squamous epithelium, 100–200 microns thick. The most superficial layer is the stratum corneum. **(C)**. Fluorescent deconvolution image (40×) of rhesus macaque endocervical epithelium. Adherens junctions (green), DAPI (blue). **(D)**. Fluorescent deconvolution image (40×) of rhesus human ectocervical epithelium. Adherens junctions (green), DAPI (blue). **(E)**. Fluorescent deconvolution image (40×) of rhesus macaque vaginal epithelium. Adherens junctions (green), DAPI (blue). Size bar is 60µm.

Fig. (2).

Histological Structures of the Male Reproductive Tract. **(A)** Macroscopic (top left) and Microscopic View (top right, bottom) of the MRT. **(A).** Representation of a flaccid, uncircumcised individual. Box represents the location of the inner foreskin (shaded), covered by the dry, outer foreskin (white). Arrow depicts where the glans and urethral opening are located. **(B).** Representation of an erect, uncircumcised individual. Box represents the location of the inner foreskin that is pulled back and exposed. Arrow depicts where the glans and urethral opening are located. **(C).** Representation of a flaccid, circumcised individual. Box represents the location of the outer foreskin that is exposed after MMC. Arrow depicts where the glans and urethral opening are located. **(D).** Representation of an erect, circumcised individual. Box represents the location of the outer foreskin. Arrow depicts where the glans and urethral opening are located. **(E).** Male reproductive tract epithelium. Includes the inner foreskin, outer foreskin, glans, and urethra near the penile opening. Tissue is composed of stratified squamous epithelium, 100–200 microns thick. The

most superficial layer, the stratum corneum, is keratinized in inner foreskin, outer foreskin, and glans tissues. **(F)**. Fluorescent deconvolution image (40×) of human inner foreskin epithelium. Filaggrin, a marker for keratinization (red), Adherens junctions (green), DAPI (blue). **(G)**. Fluorescent deconvolution image (40×) of human outer foreskin epithelium. Filaggrin, a marker for keratinization (red), Adherens junctions (green), DAPI (blue). **(H)**. Fluorescent deconvolution image (40×) of rhesus macaque urethral epithelium from the distal, penile opening. Adherens junctions (green), DAPI (blue). Size bar is 60µm.

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Fig. (3). Mechanisms of HIV Entry Across Genital Mucosal Epithelial Barriers. (top) Simple columnar epithelium. (A). Transmigration of virus through simple columnar epithelial cells. (B). Transcytosis/endocytosis through columnar epithelial cells. (C). Dendritic cell translocation across the simple columnar epithelial barrier. HIV target cells located beneath the epithelial barrier consist of dendritic cells (green), T-cells (blue), and macrophages (purple). (bottom) Stratified squamous epithelium (D). Breaks in the stratified squamous epithelium. (E). Langerhans cell translocation. HIV target cells located beneath the epithelial

barrier consist of dendritic cells (green), T-cells (blue) and macrophages (purple).
Intraepithelial HIV target cells include Langerhans cells (red).

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